# The Normal CNS: Cells, Fascicles, and Meninges

Introduction

We aren't going simply to pick up where the last lesson left off, but rather focus very narrowly on the fundamentals required to progress through this island. The goal here is to show how the embryogenesis lesson can be applied to the spinal cord, brainstem, and cortex. We've told the story of the peripheral nervous system, myelin, action potentials, and even demyelinating and muscle diseases in General Physiology. We've discussed the respiratory center in Pulmonary and baroreceptor feedback in Cardiac. We are not going to repeat that information in Neuroscience. But there is much that we simplified and moved past. Now we regain focus. This lesson is primarily about the cells of the brain and the layers that protect the brain—the meninges.

White Matter vs. Grey Matter

On gross inspection of a sectioned cortex, there is a clear delineation between what runs along the contours of the outer margin and the stuff in between. This delineation gets a little fuzzier as you get into the basal ganglia and the midbrain, but it recovers again quickly in the brainstem and cerebellum. That darker structure adhering to the contours of the brain is darker because it lacks myelin. It represents the nuclei of tracts, the location of neuron cell bodies. That is **grey matter**. The brighter contour is myelinated. It represents the axons of tracts, the location of axons. That is **white matter**.
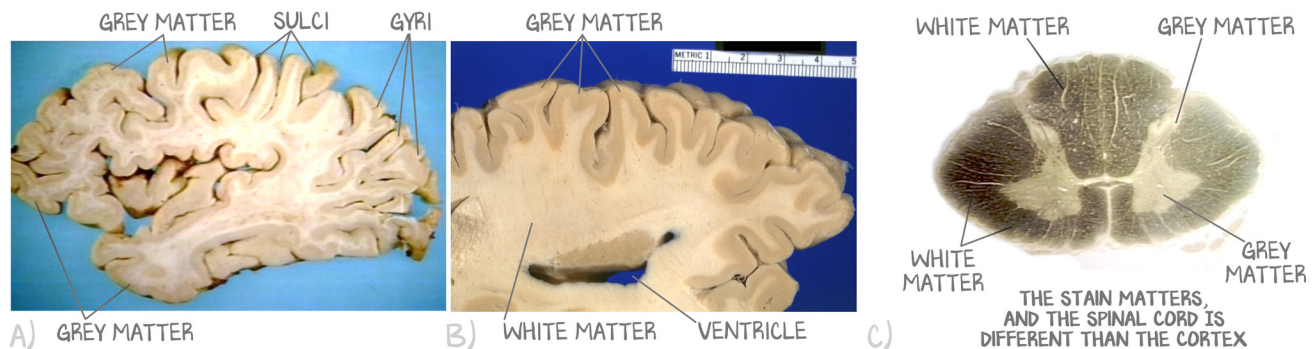
Figure 2.1: Grey and White Matter
Without staining, the outer contours of the brain have a darker appearance (grey matter), whereas the inner brain has a seemingly confluent lighter appearance (white matter). The white matter is white because of myelin, and the grey matter is darker because of the absence of myelin. The first panel is an unstained sagittal section, anterior on the left, posterior on the right. The second panel shows a nebulously sectioned, unstained brain; the exact location and slice are withheld so that you focus on the grey matter, white matter, sulci, and gyri. The third panel is included to prevent you from falling into a trap. In the cerebrum and cerebellum, the outer contours hold the cell bodies of neurons, which cause them to appear darker than their axonal tracts. In the spinal cord, white matter is in the periphery, not on the outer contours, and the spinal cord is stained by various techniques. You cannot use the darkness or lightness of a stained sample to distinguish grey vs. white matter.

Grey matter is invaginated by spaces called **sulci** (sing., sulcus), which group the grey matter into units called **gyri** (sing., gyrus). The invaginations allow for a greater surface area on which to house more neuron cell bodies (and the glial cells that care for them) without requiring greater space. This design also enables the systems that work together to be geographically associated. Gyri that don't work together and are unrelated can be separated by a sulcus.

Figure 2.2: Radiographic White and Grey Matter
A lot could be said about these MRIs. You're going to see them again, sometimes at different slices, throughout the course. These are all normal brains. Take-aways: grey matter, outer contour, cell bodies; white matter, inner mass, not grey, myelinated axons. The first panel shows a transverse section just above the third ventricle. The white matter that crosses anterior (top of image) and posterior to the ventricle represents the axons of the corpus callosum. The second panel shows a sagittal slice near the center of the axial plan, demonstrating a sulcus—the separation, the space between gyri. The final two panels show the same scan at different slices, the first being more posterior, revealing that the cerebellum has a similar arrangement to that in the cortex—outer gray matter, inner white matter.

The **central nervous system** (CNS) is the brain, brainstem, and spinal cord. The **peripheral nervous system** (PNS) is everything else—cranial nerves, peripheral nerves, and the various motor and sensory neurons that are not within the central nervous system.

Neuronal Cells of the Brain

Neurons are the neural cells of the nervous system. You've seen them before in General Physiology, and again when you studied autonomics in General Pharmacology. Neurotransmitters—acetylcholine, nitric oxide, vasoactive intestinal peptide, norepinephrine—activating different types of channels— ionotropic receptors, metabotropic receptors—with various G protein-coupled receptors (GPCR)—G_s, G_i, G_q. Axon hillocks, axons, nerve terminals, myelination, nodes of Ranvier, all the same. Inhibitory postsynaptic potentials (chloride, potassium), excitatory postsynaptic potentials (Ca^{2+}, Na^+, Na^+/K^+ mixed) are no different. Anterograde transport kinesin, retrograde transport dynein. All that stuff you already know, we don't have to go over again.

We didn't go over the different neurons' shapes, nor did we correlate them to their likely function. Neurons are classified by the number of processes extending from the cell body. **Multipolar neurons** have one axon (one output) and many dendrites (many inputs). These are usually **motor neurons** (such as the skeletal muscle neurons you have already encountered and the autonomic efferent fibers) or **integrative neurons** (don't worry about what these are yet . . . we'll get there—pyramidal cells, interneurons, and Purkinje cells).

Truly **bipolar** neurons have one axon and one dendrite. They are rare and used almost exclusively in special senses (see the Special Senses island for details). **Pseudounipolar** neurons have one axon but appear to have two. Instead, the axon branches immediately after exiting the cell body. One projection goes out to the periphery, while the other ascends to the CNS. This is seen in somatic **sensory neurons** of dorsal root ganglia.

Often tested is the fact that the neuron cell bodies are often very active in building protein. After all, most neurotransmitters are proteins, and transmembrane proteins are required to receive or deliver a stimulus. This fact makes the **Nissl bodies,** darkly staining structures in the cytoplasm around the nucleus, pathognomonic for a neuron's cell body.
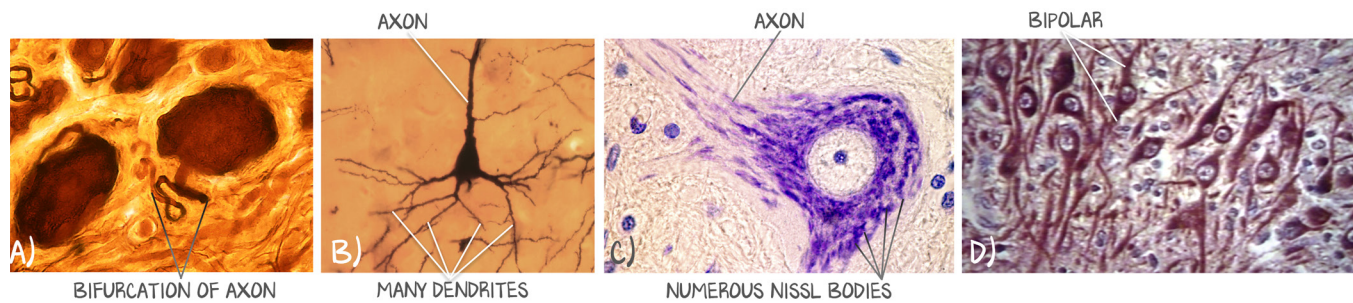
Figure 2.3: Cell Shapes
(a) Silver-stained dorsal root ganglion section showing a cell body that projects a small axon that quickly bifurcates. It splits into branches that are nearly 180 degrees from one another before moving out of the plane of visibility. (b) Silver-stained section of the cerebral cortex demonstrating a pyramidal cell. Most neurons are multipolar, and this cell demonstrates polarity. An axon projects towards the top of the image. Below the cell body are many dendrites. Dendrites receive synapses from other cells. If those synapses depolarize the cell, the electrical signal leaves the cell along the axon. (c) Motor neuron stained to show Nissl bodies. (d) Taken from a retina and stained for the bipolar interneurons, you can see that it isn't always a perfect polarity, but in general, one projection with dendrite and another projection as the axon.

Neuron Fascicles

Axons in the **PNS** are organized into bundles called **peripheral nerves** when they come from the spinal cord, and **cranial nerves** when they come from the brainstem. Each axon is surrounded by its own connective tissue, the **endoneurium**. Individual axons are bundled together and surrounded in **perineurium**. The bundle itself is called a fascicle ("bundle" and "fascicle" are interchangeable). Bundles of fascicles—multiple fascicles—are wrapped in **epineurium** to make a **nerve**. To maintain parallels to the central nervous fascicles, we want you to learn that only axons of a similar kind will exist in a fascicle. Perineurium surrounds the axons of a given tract. What makes peripheral nerves so special is that they carry fascicles of many tracts. For example, axons of motor neurons are carried within a motor neuron fascicle, carrying only motor neuron axons. The neighboring fascicle could comprise somatosensory axons or autonomic efferent fibers, but that fascicle will consist of only one kind of axon.
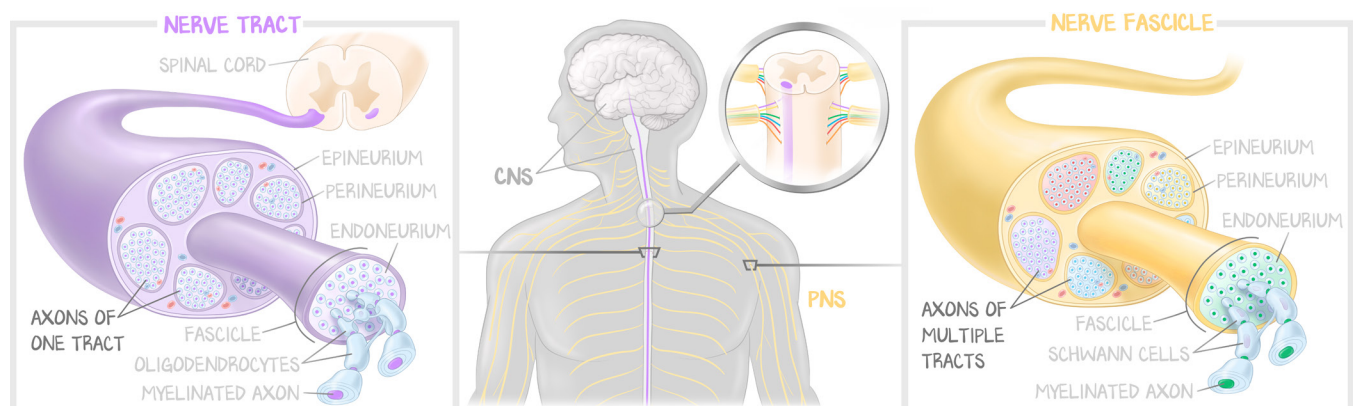
Figure 2.4: Neurons, Fascicles, and Nerves; CNS vs. PNS
In the central nervous system—the spinal cord in particular—only axons of a given type, those that belong to the same tract, ever hang out together. They developed from different plates—alar or basal. The locations where their cell bodies reside, the cranial nuclei, are physically distinct. So, too, are their tracts. There are sensory tracts and motor tracts. And even then, a specific sensory tract (there are many) travels only within a fascicle of one type of axon. Within the central nervous system, tracts don't mix. In the peripheral nervous system tracts do mix, but only functionally, as the axons of dissimilar tracts—being separated by dissimilar fascicles—don't bump into the axons of another tract.

Support Cells of the Brain—Neuroglia

The neuroglia, or **glial cells**, of the central nervous system support the neurons. These are the astrocytes that keep the blood-brain barrier tight, the oligodendrocytes that do the myelinating, the ependymal cells that line ventricles, and the microglial cells that act as resident macrophages. Glial cells represent about half the volume of the brain and are more numerous than neurons. Unlike neurons, which have little capacity to replace themselves when lost, glial cells can proliferate throughout life. An injury to the nervous system is the usual stimulus for proliferation, histologically termed gliosis. All glial cells derive from neuroectoderm, except the resident macrophages (microglial cells), which derive from mesoderm.

Unlike most organs whose cells use a basement membrane to line an epithelium and separate it from the extracellular matrix, the CNS is relatively devoid of such basement membranes. They exist where there are blood vessels (the blood vessels' endothelial cells' basement membrane) and where ependymal cells line CSF-filled cavities. This freedom ensures that the axons of neurons are always kept separate from one another, and enables one glial cell to influence multiple axons.

Astrocytes are the keepers of the blood-brain barrier; they modulate neuronal activity, and likely supply the neurons with nutrients from the bloodstream, much as osteocytes do for each other in the osteon. More on these guys in the next section.

Ependymal cells line ventricles and aqueducts—all of the inside-the-brain CSF-filled spaces (as in, they do not line the subarachnoid space, which is also CSF-filled). They are the only true epithelium of the CNS. They are a ciliated simple columnar epithelium with tight junctions that prevent paracellular movement of ions. Their job is to keep the CSF out of the parenchyma, and sometimes (as discussed in the next lesson) secrete CSF (choroid plexus) or reabsorb it (arachnoid granulations). They are small. The guardians of the blood-brain barrier, the astrocytes, ensure a tight seal against the ependymal cells the way they do the endothelial cells of the vasculature.

Oligodendrocytes are the Schwann cells of the CNS—they are responsible for myelinating axons. But very unlike the Schwann cells that myelinate the peripheral nerves, **one oligodendrocyte myelinates many axons**. The projections of cytoplasm are kept narrow and proximal to the cell until the myelination begins, and then they widen out. This is to enable axons to be packed together and additional oligodendrocytes to myelinate axons nearby to it. The same **internodal myelin sheath** and the **nodes of Ranvier** you are familiar with are present here in the CNS (there are small differences, but for all intents and purposes, you can treat them the same).
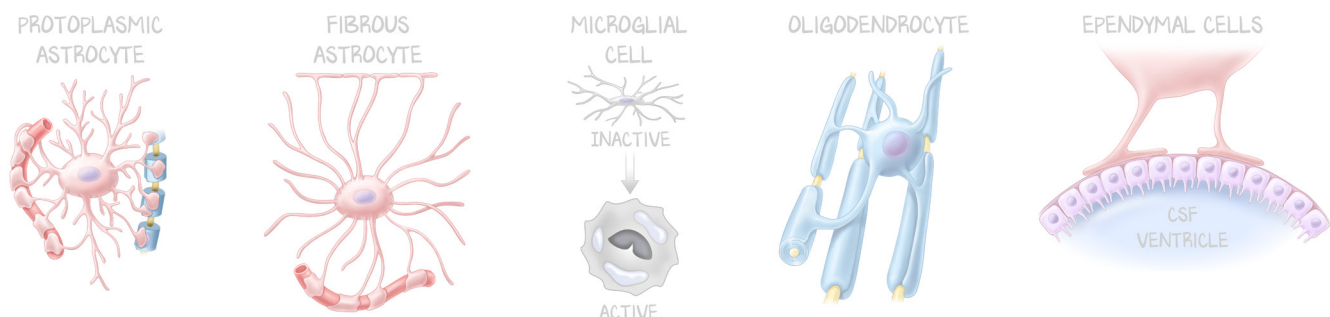

Figure 2.5: Illustrations of Glial Cells

Microglial cells are indeed micro (they are small) and glial (not neurons). That doesn't tell you anything about what they do, though. These are the **resident macrophages** of the CNS. They are **phagocytes** and **antigen-presenting cells**, just like any other resident macrophage—except these guys change shape to accommodate the specialty of the CNS. In the **resting position**, they look nothing like the

macrophages you know; they have long, slender processes that enable them to snake between axons and take up as little space as possible, leaving room for axons and glial cells. When activated, however, they become very similar in shape and size to macrophages. Being resident macrophages, these are the only glial or neuronal cells that derive from **mesoderm**. They are macrophages and follow the macrophage maturation pathway from the granulocyte-monocyte colony-forming unit.

Astrocytes

Most astrocytes in the brain are traditionally subdivided into fibrous and protoplasmic types. **Fibrous** astrocytes (found mainly in white matter) have long, thin, and well-defined processes, whereas **protoplasmic astrocytes** (found mainly in gray matter) have shorter frilly processes. Since they likely serve similar purposes (everything you are about to read), we're just going to say "astrocyte" from here out. Astrocytes are always evenly spaced. In cortical regions, the dense processes of an individual astrocyte define its spatial domain, into which adjacent astrocytes do not encroach. Astrocytes express **glial fibrillar acidic protein (GFAP)**. But use caution—although mature differentiated astrocytes are the only glial cells to make GFAP, undifferentiated malignancies that form from glial cell precursors will all express GFAP. In physiology, GFAP identifies astrocytes. In pathology, GFAP identifies glial cells in general.

Astrocytes and the blood-brain barrier are responsible for keeping everything that should be out of the CNS, out of the CNS. Individual axons being extremely fragile, the impulse of action potentials so precise, and the electrical activity of all neurons being determined by other neurons' activity, there must be a strictly maintained extracellular matrix. The way this happens is by having capillaries that are not just continuous capillaries, but with continuous tight junctions (extra-tight compared to normal) added to neighboring endothelial cells, making them the least leaky possible, and by adding a second plasma membrane seal on the brain side of the blood vessel's basement membrane—astrocyte pedicles. Any one astrocyte will not envelop a capillary by itself (it doesn't behave as an "endothelial oligodendrocyte"), but any blood vessel will be completely encased in the pedicles of neighboring astrocytes. Whereas in Renal we saw fenestrated capillaries admitting molecules to the basement membrane and podocyte pedicles providing a selective filtration barrier, it is the opposite in the CNS. The capillaries shut any gaps tighter than usual, and the astrocytes restrict the movement of anything that isn't a small molecule (CO_2, O_2, glucose) or lipophilic.

Astrocytes feed neurons. It is suspected, but not proven, that the astrocytes behave toward each other as osteocytes do in an osteon. Encased in calcified bone, nutrients cannot diffuse from the osteonal canal to the outermost lamella of the osteon. Instead, gap junctions connect the canaliculi—thin cytoplasmic projections—of one osteocyte to the next. Osteocytes and astrocytes even have a similar appearance— many thin projections in all directions. But what we do know is that astrocytes envelop neurons, meaning the extracellular space of the neuron is controlled by the astrocyte. The astrocyte **cannot deliver glucose** to the neuron, but astrocytes can deliver lactic acid and glycogen, both forms of energy the neuron can use, providing a secondary reserve for energy that neurons cannot obtain other ways (as discussed in Biochemistry: Metabolism #2: *Glucagon vs. Insulin*). This **substrate buffering** enables astrocytes to facilitate their local axons or somas.

Astrocytes also modulate potassium. Astrocytes are able to take up potassium from the local axonal extracellular fluid. Potassium is indicative of action potentials and neuronal activity. The resting membrane potential for the neuron is about –65 mV. For the astrocyte, –90 mV (exactly the equilibrium potential for potassium). In this way, the astrocyte maintains the extracellular potassium for a more favorable environment for neuronal discharge, and potassium may be the signal for the astrocyte to release glycogen and lactate for its segment of the neuron. We don't want you to focus on the specific channels, just that astrocytes pick up potassium. But not only do they pick it up from their extracellular microenvironment, but **they also share it with each other**. Linked by gap junctions, astrocytes work as a syncytium, passing materials between them, and buffer potassium. This **spatial buffering** enables the regulation of action-potential behavior.

Astrocytes modulate neurotransmitters. Astrocytes have neurotransmitter receptors, take up neurotransmitters, and release neurotransmitters. They are unable to have an action potential themselves, but they are involved in the modulation of neuron behavior. We'll explore this in more detail when we talk about glutamate and $GABA_A$ receptors later in the course.

Astrocytes reinforce the CSF barrier. Just as the astrocytes envelop the basement membrane of endothelial cells, preventing the filtration of molecules into the brain extracellular fluid, so too do they do it to the simple squamous epithelium of the pia mater, forming the **glia limitans**. This prevents the intrusion of cerebrospinal fluid back into the brain parenchyma from the subarachnoid space. Astrocytes do something similar to ependymal cells lining the ventricles, but with a much less pronounced histological consequence. The idea is that astrocytes plug any holes in the capillaries, the pia mater, or the ependymal layer.
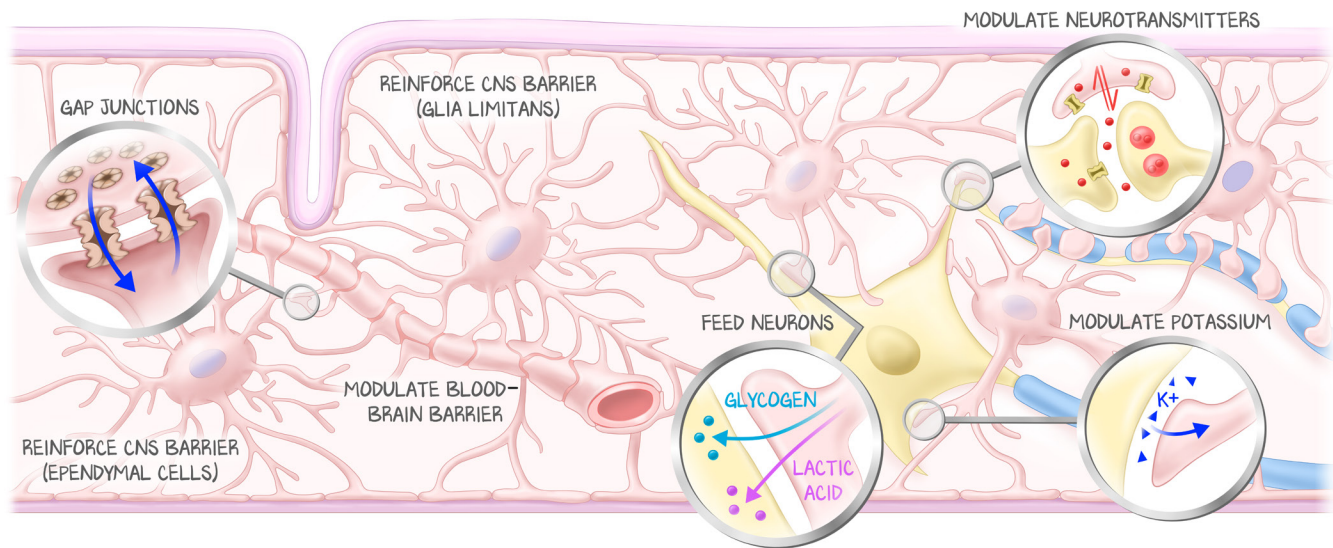
Figure 2.6: All About Astrocytes
This illustration is a summary of astrocyte functions in a stylized form rather than an accurate anatomic depiction.
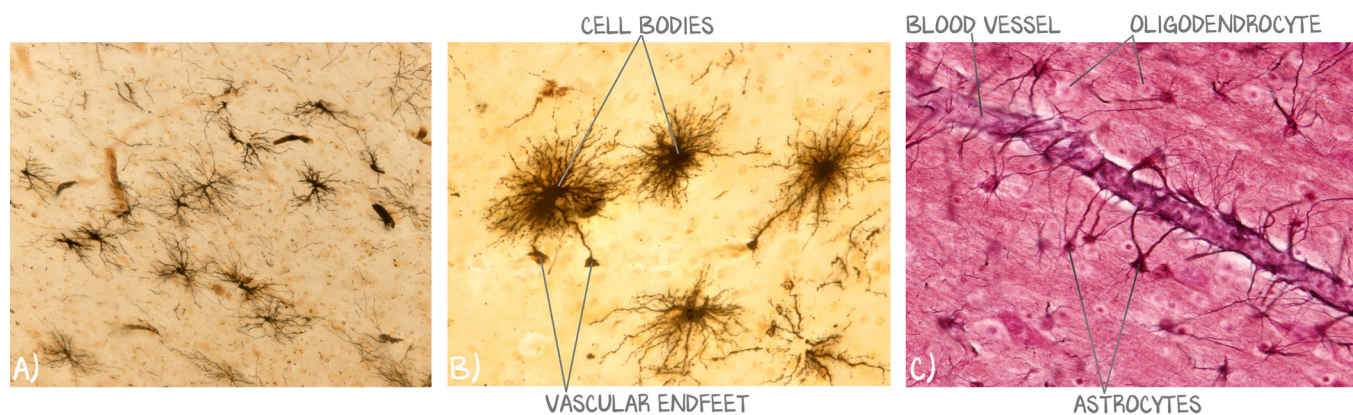
Figure 2.7: Astrocytes Under the Microscope
(a) Low-powered view of silver-stained white matter demonstrating fibrous astrocytes with long processes. (b) High-powered view of silver-stained grey matter revealing pilocytic astrocytes with visible vascular endfeet. Their processes are much more numerous than those of the fibrous astrocytes in panel a. (c) White matter showing how astrocytes regulate blood vessels. Multiple astrocytes manage any one region of the vessel. Oligodendrocytes are also visible.

That was the cells. Let's change gears and talk about what happens just outside the brain parenchyma— the meninges.

Meninges

Just outside the glia limitans are several layers that separate the brain parenchyma from the atmosphere. Between the skull (bone) and the glia limitans are three histological layers. Here in the brain, histological layers are called **meninges**. These layers were named before SEM and TEM were even thought to be things. We are going to describe the layers of the meninges accurately, then show you what many people think.

The first structure between brain parenchyma is the **leptomeninges**. It is one thing with three sublayers, working from the brain out—the pia mater, the subarachnoid space, and the arachnoid mater. The **arachnoid mater** is a layer of squamous cells, 7–10 cells thick. **Trabeculae** cross the subarachnoid space and connect the arachnoid mater layer to the pia mater layer. The **pia mater** is a simple squamous epithelium at the bottom of the subarachnoid space. It is an extension of the arachnoid mater, and it serves to provide the basement membrane onto which astrocytes form the glia limitans. The same fibroblast-like cells that are the arachnoid mater are also the fibroblast-like cells that traverse the subarachnoid space and the fibroblast-like cells of the pia mater. The trabeculae not only serve as a mechanism for more fibroblast-like cells to renew the cells of the pia mater, but also act as a better suspension system than a simple sac of fluid. That means the leptomeninges is one common structure made of fibroblast-like cells. If the brain were traveling in one direction and then suddenly stopped, a fluid-filled cavity would give way to the brain. The trabeculae all around the brain act more like a spring—pulling back while maintaining resistance.

The arachnoid mater stays adherent to the dura mater above it, running as a sheet of cells along the inner contour of the dura mater. The **pia mater follows the brain**. As the sulci of the brain dip and the gyri rise, the pia mater stays with the parenchyma. Because the pia mater follows the contours of the brain, and the arachnoid mater doesn't change its contour, the trabeculae to the dips in the sulci must be inherently longer. The cerebrospinal fluid fills the **subarachnoid space** and thus will fill in the sulci.

Also running within the subarachnoid space are blood vessels. The endothelial cells have tight junctions, and specialized cells of the arachnoid mater perform the same purpose as the glia limitans, preventing the leaking of blood or its contents into the CSF. If a blood vessel penetrates the brain parenchyma, it always has a layer of pia mater going with it.

The **subarachnoid space** is named because it is under the arachnoid mater. We'll get into the details in the next lesson, but CSF acts to cushion the brain. It flows from the ventricles into the subarachnoid space and eventually is drained by a structure at the top of the head. Blood vessels for the parenchyma also travel in this space. **Blood vessels travel with the SAS** and **CSF travels in the SAS**. Veins, lined with the pia mater, traverse the SAS to enter dural sinuses. Arteries, traveling in the SAS, penetrate the parenchyma lined in pia mater.

The leptomeninges are derived from **neural crest cells**.

On the outside of the arachnoid mater is the **dura mater**. The dura mater is a thick, inelastic membrane that forms an outer protective envelope around the brain, on top of the arachnoid mater and below the skull. The dura has one layer. But every once in a while, a vessel will wedge itself into the middle of the dura mater. When it does, it appears to have an ostial layer and a meningeal layer. The dura mater is made from mesoderm, induced to form the dura by the replicating neural tube.

Both the leptomeninges and the dura mater encase the central nervous system and the spinal cord.
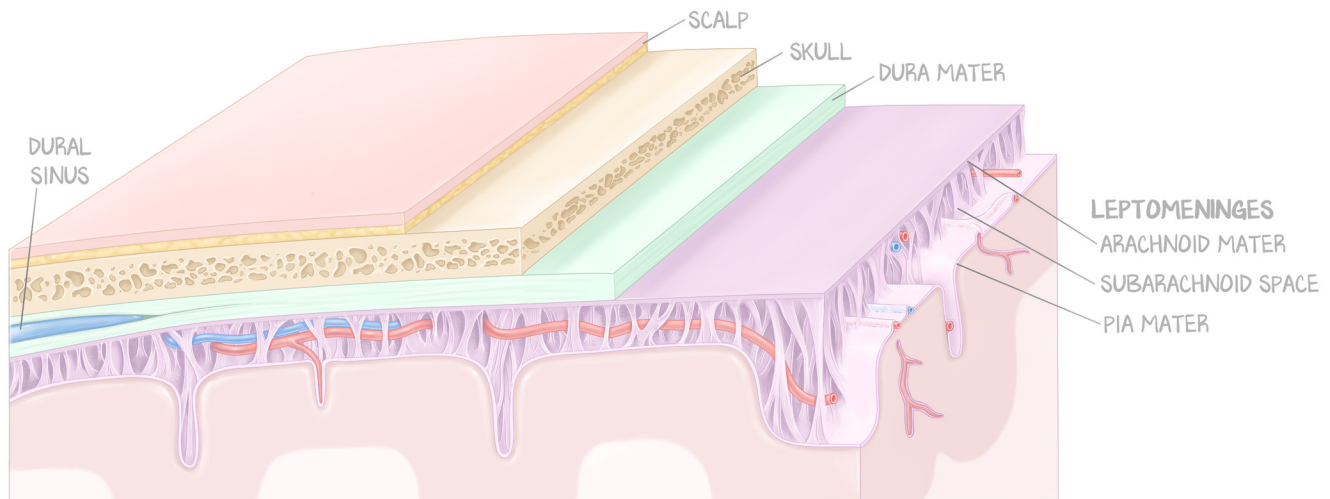
Figure 2.8: The Meninges
From the skin in towards the parenchyma, the skin of the scalp covers the bones of the skull. Once under the bones, the structures are now intracranial, within the cranial cavity bounded by the cranium. The dura mater separates the bone from the outermost layer of the leptomeninges, the arachnoid mater. The arachnoid mater, pia mater, and trabeculae between those layers represent a passageway for the cells of the pia mater to reave the pia mater from the arachnoid mater. Cerebrospinal fluid courses within the gaps between trabeculae. And traveling in the subarachnoid space, surrounded by cerebrospinal fluid but separated from the fluid by cells of the arachnoid mater, blood vessels run. There is no space between the dura mater and the arachnoid mater, and no space between the dura mater and skull. They are not continuous, so each represents a potential space. The pia mater hugs the contours of the parenchyma and encases blood vessels as they penetrate parenchyma.
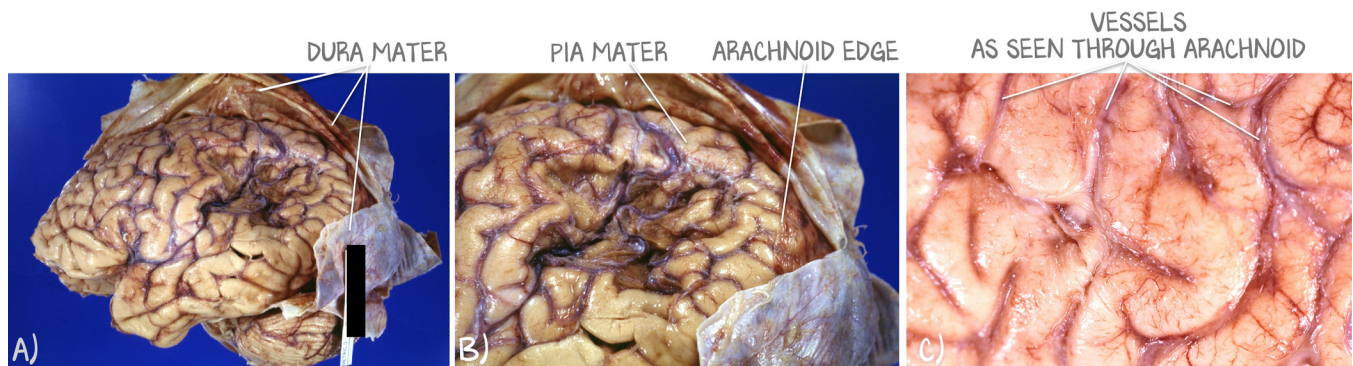
Figure 2.9: Visualizing the Leptomeninges
(a) Whole brain with dura mater and pia mater dissected. The divot above cerebellum is a product of a lesion (not present). (b) Higher magnification demonstrating that the hard, white dura mater is opaque and obvious, whereas the arachnoid layer is essentially see-through. (c) Brain of a patient with meningitis used to demonstrate the blood vessels through the arachnoid mater, showing how thin a layer the leptomeninges is.

Citations

Figures 2.1a, 2.1b, 2.1c, 2.9a, 2.9b, 2.9c: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.

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